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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,932	THEOBALD ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending and are subject of this office action. Receipt is acknowledged of a preliminary amendment filed on 03/03/2006 in which claims 1-15 were amended and new claims 16-17 were added.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 recites the limitation "present therein" in the penultimate line of the instant claim. There is insufficient antecedent basis for this limitation in the claims and it is unclear as to exactly where the phrase "present therein" is referring to if it the entire composition or just the polymer layer. It would be remedial to amend the claims to provide a clear antecedent basis for the term "present therein".

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,3, 4, 5, 6, 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Beier et al (WO 03/015779 as translated by US 2004/0247656)

Beier et. al discloses an active-ingredient –containing matrix-controlled transdermal therapeutic system (TTS) for the use of pramipexol, ropinirole, pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivative thereof (abstract). Beier discloses that a matrix-TTS comprising pramipexole, ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates, especially solvent-containing polyacrylates or an polyisobutylene is used [0015]. A matrix-TTS according to Beier consists of an impermeable cover layer, one or more self-adhesive matrix layer(s) containing the active-ingredient and where applicable permeation enhancers/solubilizer, or one or more matrix layer(s) that are coated with a pressure-sensitive adhesive, and a peel off protective layer and the active ingredient contained in the matrix is pramipexole, ropinirole its salts or derivatives [0016]. The amount of Pramipexole, ropinirole, salts or derivatives used in the transdermal therapeutic system of Beier ranges from 2-15% by weight of the matrix [0018]. The higher end of this range 15% falls within the range claimed in instant claims 1 and 14 and thereby anticipates the range. Beier discloses that active ingredient to be pramipexole, ropinirole or pharmaceutically acceptable salts of pramipexole or derivatives, solvates with the active ingredients such as hydrates and alchoholates [0017]. Beier discloses that for pressure-sensitive adhesive layer, a pressure-sensitive adhesive based polymer such as polyurethane, polyisobutylene, polyvinylether, silicone, polyacrylate or a mixture thereof can be selected [0020] For the

matrix, matrix formers customary in medicine are used e.g. polyacrylates and polyisobutylene and the matrix formers based on polyacrylates may be any desired homopolymers, copolymer or terpolymer consisting of various acrylic acid derivative, where applicable with vinyl acetate [0021-0022]. Beier discloses various monomers to be used in his invention which includes esters of acrylic and methacyrlic acids such as butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, etc that may be polymerized individually or in admixture [0024]. In addition functional monomers that are compolymerisable with the acrylates and methacyrlates include hydroxyethyl acrylate, hydroxypropyl acrylate can be used too[0025], Further more Beier discloses examples wherein the composition of a self-adhesive matrix transdermal therapeutic system for pramipexole includes pramipexole , Copherol and Durotak 2287 [0030] and [0048] *Durotak 2287 is the polymer recommended by the applicant in the instant specification and used in the instant examples (page 7, line 34 to page 8. line 5 , example 1 and 2 on page 12 of instant application).* Applicant discloses in the instant specification that this specific polymer comprises vinyl acetate and is stable and well tolerated pressure-sensitive adhesive polymer. Since the same polymer is used in the Beier reference, the characteristics and compositions of the polymer is carrier with it which includes the vinyl acetate concentration. Accordingly the concentration of vinyl acetate claimed is anticipated by Beier.

Accordingly, instant claims 1, 3, 4, 6, 7,14 and 16 are rejected under 102(e) as being anticipated by Beier et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beier et al.(WO 03/015779 as translated by US 2004/0247656) in view of Zierenberg et al, (US 5112842) and Patel et al (WO 96/39136).

Beier et. al teaches an active-ingredient containing matrix-controlled transdermal therapeutic system (TTS) for the use of pramipexol, ropinirole, pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivative thereof (abstract). Beier teaches that a matrix-TTS comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates, especially solvent-containing polyacrylates or an polyisobutylene is used [0015]. A matrix-TTS according to Beier consists of an impermeable cover layer, one or more self-adhesive matrix layer(s) containing the active-ingredient and where applicable permeation enhancers/solubilizer, or one or more matrix layer(s) that are coated with a pressure-sensitive adhesive, and a peel off protective layer and the active ingredient contained in the matrix is pramipexole, ropinirole its salts or derivatives [0016]. The amount of Pramipexole, ropinirole, salts or derivatives used in the transdermal therapeutic system of Beier ranges from 2-15% by weight of the matrix [0018].Beier teaches that active ingredient to be pramipexole, ropinirole or pharmaceutically acceptable salts of pramipexole or derivatives, solvates with the active ingredients such as hydrates and alchoholates [0017] Beier teaches that for pressure-sensitive adhesive layer, a pressure-sensitive adhesive based polymer such as polyurethane, polyisobutylene, polyvinylether, silicone, polyacrylate or a mixture thereof can be selected [0020] For the matrix, matrix formers customary in medicine are used e.g. polyacrylates and polyisobutylene and the matrix formers based on polyacrylates may be any desired homopolymers, copolymer or terpolymer consisting of various acrylic acid derivative, where applicable with vinyl acetate [0021-0022]. Beier

teaches various monomers to be used in his invention which includes esters of acrylic and methacyrlic acids such as butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, etc that may be polymerized individually or in admixture [0024]. In addition functional monomers that are compolymerisable with the acrylates and methacyrlates include hydroxyethyl acrylate, hydroxypropyl acrylate can be used too[0025], Further more Beier teaches examples wherein the composition of a self-adhesive matrix transdermal therapeutic system for pramipexole includes pramipexole , Copherol and Durotak 2287 [0030] and [0048]. *Durotak 2287 is the polymer recommended by the applicant in the instant specification and used in the instant examples (page 7, line 34 to page 8. line 5 , example 1 and 2 on page 12 of instant application).*

The teachings of Brier differs form the instant application in that Brier is silent as to the Pramipexol being in the form of and S (-) enantiomer, where in the pramipexol is present in the proportion of between 10-25 % by weight and finally the delivery rate of pramipexol is 0.1-10 or 0.5-4.5 mg/ day.

These deficiencies are taught by Zierenberg et al and Patel et al.

Zierenberg et al teaches transdermal administration of 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole (Pramipexole) or the (-) enantiomer thereof and transdermal systems containing these active substances (abstract). Zierenberg teaches that transdermal administration of Pramipexole, doses of 2 mg per day can be administered without an orthostatic side effects occurring in the patient, which corresponds to 10 times the amount which can usually be administered by oral

application of the substance (col.1, lines 30-38). Zierenberg additionally teaches that although the solution to his invention is not limited to the use of a specific transdermal therapeutic system, provided the system ensures an adequate release of active substance-systems which have an active substance reservoir consisting of an emulsion polymerized polyacrylate are preferred according to his invention. Using such systems Zierenberg teaches that it is possible to administer 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothaizole or the (-) enantiomer thereof in a dose of 0.5-5 mg per day without any orthostatic side effects being observed (col.1, line 49 to col.2, line10, claim 9). Zierenberg additionally teaches that his system consists of a backing layer which is impervious to the active substance and is simultaneously as a covering plaster to secure the system to the skin, a reservoir containing the active substance and a removable protective film which protects the system before it is ready to be used and the preferred carrier material polyacrylate is the type marketed as Eudragit NE. The proportion of the active substance in the reservoir is between 5-30% preferably between 7-15% by weight (col.2, line 11-23).

Patel et al. teaches transdermal formulations comprising ropinirole for use in treating Parkinson's disease (abstract). Patel teaches that the transdermal formulation offers the advantage of a more convenient mode of administration of the drug substance, thereby potentially enhancing patient compliance and in addition, drug substance is released in a more controlled fashion, over a prolonged period, offering potential therapeutic advantages (page 1, lines 29-32). Patel teaches that the transdermal system of his invention will provide a steady rate delivery, or alternatively a

comparmentalized rate controlled system and a suitable target skin flux will be in the range 5-2 preferably 10-15 ug/cm^2/hr (page 3, lines 10-13 and page 7, claims 2). Patel teaches the transdermal formulation to be provided in a unit dose form, in a range of dosage amounts, for instance to allow for titration of an individual patient's drug requirement and a suitable dose may be obtained by combining different strength formulation. Additionally, Patel teaches a unit dose form to provide sufficient drug substance for a 24 hour period to permit once-a-day application of the formula (page 3, lines 21-28).

Both Pramipexol and Ropinirole are non-ergoline dopamine agonists commonly used in the treatment of Parkinson's disease as evidenced by D.J Brooks (J. Neurol.Neurosurg. Psychiatry, 2000; 68; 685-689) who teaches on page 687, under the heading Non-ergoline Agonists that ropinirole and pramipexole are both new dopamine both of which act as agonists of D2-type receptors. Therefore, Pramipexol and Ropinirole are functional equivalents. Additionally, Beier et al, teaches the use of these two drugs together in a transdermal system providing a suggestion that one of ordinary skill in the art could use pramipexol in place of Ropinirole in the transdermal system taught by Patel.

With regards to the limitation claimed in instant claims 1, 6, 14 and 16 which claims ranges of the weight of the active ingredient and the weigh of vinyl acetate in the formulation, optimizing the range at which the most optimal results are obtained is well within the capabilities' of one of ordinary skill in the art. Additionally, It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not

inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Because Beier teaches that a matrix-Transdermal Therapeutic System comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates is used, Zierenberg teaches the reduction of orthostatic side effects in delivering pramipexol as transdermal therapeutic form and Patel teaches that transdermal forms offers several advantages over oral administration such as patient compliance and controlled delivery of the drug, it would have been obvious to one of ordinary skill in the art at the time of the instant invention that transdermal therapeutic system comprising pramipexol with in an active –ingredient containing polymer layer with at least one pressure sensitive adhesive polymer. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success based on the state of the art at the time of invention that such a transdermal therapeutic system would be an effective system for delivery of pramipexole as it offers longer duration of constant delivery and higher stability.

With regards to limitations claimed in instant claim 11 wherein the drug is delivered continuously to a patients' skin over a period from 4 to 7 days, and limitations in the instant claims 12 and 13 of the active ingredient being released over a period between 24 hours after administration to 72 hours or 168 hours, designing transdermal therapeutic systems for delivery of drugs continuously for desired time period at the rate is well known in the art as evidenced by Scheindlin (Molecular Interventions 4: 308-312 (2004)) who teaches on page 308, the scopalamine patch is worn behind the ear and

releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically, the fentanyl patch acts for seventy-two hours, providing long lasting pain relief and an estrogen-progestin contraceptive patch which has to applied once a week. Accordingly, one of ordinary skill in the art would be able to formulate the transdermal therapeutic system for pramipexol as taught by Beier, Zierenberg and Patel to have the desired release profile ranging from once a day to once a week administration.

Conclusion

Claims 1-17 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SAVITHA RAO
Examiner
Art Unit 1614

/Ardin Marschel/
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